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"DOMINANT" AND "RECESSIVE" SPOTTING IN MICE

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INTRODUCTORY

THE inheritance of spotting has long proved of interest to animal geneticists. The nature of spotting is such as to afford an excellent chance to observe quantitative fluctuation and variations of very minute size. Furthermore, the fact that spotted varieties are found in all the rapidly breeding smaller domesticated mammals has led to a widespread investigation of its phenomena of inheritance.

One of the most clean-cut and constant types of spotting which has been studied is that of the "hooded" pattern in rats. This character was studied independently by Doncaster (1905) and by Castle and McCurdy (1907). All these observers agree that this form of spotting is due to a recessive Mendelizing unit which gives a 1:3 ratio in crosses with self-colored races.

In mice there has been no such well-localized pattern recorded and a series of spotted forms has been described which vary from black-eyed whites on one end of the series to heavily colored animals having only a few white hairs on the forehead or on the belly at the other extreme.

Cuénot, who did considerable work on the inheritance of spotting in mice, came to the conclusion that spotting is due to a group of recessive spotting factors which he describes as *p*1, *p*2, *p*3, *p*4, etc. His figures, however, show a single unit character difference as 3:1 and 1:1 ratios prove.

Up to 1908 all the spotting in mice was classed as recessive to solid-colored coat. At that time, however, Miss Durham described the appearance of dominant spotting in addition to the recessive form which she also had experimented with. Such a dominant form of spotting is supposed, by Bateson, to be due to the addition of some factor for restriction of pigment formation in certain areas. This produces a dominant form of spotting as contrasted with the recessive type, which, he holds, is due merely to the loss of the ''self'' factor.

Hagedoorn (1912) gives data to show that the dominant form of spotting occurs in mice and in addition considers it as produced by a factor analogous to that which produces the dominant ''English'' spotting in rabbits.

The object of this paper is to present certain evidence concerning the nature of dominant and recessive spotting in mice; to discuss in its light the results of the above-mentioned investigations; and to criticize one additional point in Hagedoorn's work with mice.

EXPERIMENTAL

Materials.—Among several wild mice caught during the spring of 1911 was one individual with a white spot or ''blaze'' on the forehead between the eyes. This spot or ''blaze'' was about one quarter of an inch in length and one eighth of an inch in width. This mouse, an adult male, was transferred to a breeding cage and a series of experiments was started to determine whether the ''blaze'' character was inherited and, if so, in what way. As at that time no adult wild females were available from unrelated stock the wild ''blaze'' male (*S*1) was crossed with a female from a dilute brown race. In many ways this dilute brown race was the best possible material for such a cross. It was very closely inbred, being descended from a single pair of animals, progeny of which had been free from out-crossing for more than a year. Further, it had never given, nor has it ever given in hundreds of young, an animal with the slightest trace of a spot, even on the tail, where white bands are frequently seen in wild mice. Besides this the race was vigorous and active and yet easy to handle.

RESULTS

As a result of mating *S*1 "blaze" with a female of this dilute brown race, two litters, totalling eight young, were produced. All these young were self-colored without a trace of white, and, as expected, all resembled the male in coat color.

The F_1 generation selfs were then crossed in two ways, (1) *inter se* and (2) with animals of the dilute brown self race to which their mother belonged. It is hoped that a detailed account of all the matings made may be published later, but for the present purposes certain of the crosses under the first heading will suffice.

When F_1 was crossed *inter se,* two sorts of young were produced, namely, those with white and those without. While all of the latter type may be classed as self, the former were of two general sorts: (1) those with a "blaze" as large or larger than that of *S*1, these we may call "blaze" animals; and (2) those with only a *few white hairs* on the forehead, which we may call few white-haired (f.w.h.) animals.

The exact numbers in this cross were

Parents	Offspring		
	Self	F.W.H.	Blaze
*S*6 × *S*5—*S*8	11	3	3
*S*19 × *S*8	10	13	6
*S*18 × *S*8	3	1	2
	24	17	11

When the F_2 few white-haired animals were bred together they produced three types of young: *few white-haired, blaze* and *self,* as follows.

Parents	Offspring		
	Self	F.W.H.	Blaze
3,030 × 3,028	11	6	—
3,043 × 3,028	5	5	1
	16	11	1

One further fact is also of interest. Various descendants of F_2 "blaze" animals, which should breed as recessives, have given the following results. The generation numbers may be disregarded as they refer to another method of classification. It is to be remembered that the parents in the tabulation given below, are all "blaze" in character.

Generation	Young Produced				
	Blaze	Blaze and Ventral White	F.W.H.	Self	Total
F_3B........	33	6	4	1	44
F_4B........	157	60	27	3	247
F_5B........	70	53	5	0	128
F_6B........	9	6	0	0	15
Total.....	269	125	36	4	434

If the "blaze" is a true Mendelian recessive we should expect all 434 offspring to have some white on them. The figures show that 430 of the 434 are of this type; that is to say, approximately 1 per cent. are self.

It is possible to account for the occasional production of selfs even if the "blaze" character is a true recessive, if we supposed that there are supplementary factors which may influence color development; and it is quite conceivable that such is the case.

The chief point of interest in the crosses given above is that while spotting behaves in F_1 *as a recessive, certain of the* F_2 *spotted individuals fulfil the requirements of dominant spotting by producing self offspring.*

The spotting came from a single individual and can scarcely be considered to be of two distinct types.

We may now consider the bearing of these results on the work of Miss Durham and Hagedoorn.

Miss Durham's Results

Miss Durham (1908) gives a detailed account of a recessive type of spotting in mice. The numbers she obtained are extensive, and the case seems well established, coming as it does in corroboration of the work of Cuénot, Darbishire and others. In the same papers she records the occurrence of a *dominant* spotted type of mice. Bateson (1909), commenting on the case, compares it with the dominant "English" spotting in rabbits but also agrees that, in the case of mice, there is no criterion to enable one to distinguish somatically between the dominant and recessive forms. This, of course, is not the case in rabbits where the "English" pattern differs visibly from the "Dutch" spotting, which Hurst (1905) found to be recessive to self. Bateson also considers that the case of dominant spotting in mice, reported by Miss Durham, is the result of a different spotting factor from that producing recessive spotting.

In terms of the presence and absence hypothesis this means that the dominant form possesses a factor for restriction of pigmentation *which self forms lack.* This fact becomes of interest when Miss Durham's experimental results are closely examined.

In the race which gave rise to the dominant spotting the following conditions are seen.

A sooty yellow spotted mouse of unknown origin was crossed with a black-eyed white (spotted) animal (of Atlee's strain). Among other progeny was obtained a black-eyed white mouse with "agouti ears." This mouse, No. 21 (spotted), was crossed with an albino (carrying chocolate), No. 35, and gave among its progeny No. 69, *a black self mouse.* This black animal, No. 69 was crossed with an albino (carrying chocolate), No. 34, and from these two individuals came the dominant spotted race.

Now inasmuch as No. 34 and No. 35, the albinos, were not supposed to carry spotting, the dominant spotting must be considered as probably coming from No. 69, a *black self animal.* We know that *this animal must carry spotting as a recessive character* since its parent, No. 21, was spotted.

If, therefore, this animal was the progenitor of the dominant spotted race, and if he carried a recessive spotting, as it seems certain he did, we must suppose that one of three things has happened to the recessive spotting which he carried.

1. It may have been completely lost, failing to manifest itself in his germ cells.

2. It may have continued to exist and to be inherited together with the dominant type of spotting.

3. It may have been changed to a so-called "dominant" type of spotting simply by the nature of modifying supplementary factors which it encountered during ontogeny.

The first two cases necessitate the origin of the "dominant" spotting by a mutation in no way connected with the previous recessive spotting. In the first case, moreover, we should have to suppose the disappearance of the recessive spotting character in a manner entirely contrary to any principle of Mendelian heredity. In the second case the occurrence of the two types of spotting side by side in the same litters of young would so complicate the experiments that analysis would be difficult if not impossible, on Miss Durham's results.

There is good reason to believe that the third possible explanation is the correct one. It accounts for the formerly "recessive" type of spotting. It presupposes no fundamentally different appearance of the two types of spotting. Moreover, it is very probable that the albino race brings in the modifying factors necessary to give the apparent change in the type of spotting. The addition of a factor as presupposed by the presence and absence hypothesis is not proved by the results obtained nor is it necessary to account for them.

That the presence and absence hypothesis does not apply to all cases of spotting is seen in the case of the "blaze" mice in my experiments. Here, if F_1 animals had been given me as a starting point for experimentation, I should conclude the spotting to be recessive, while if F_2 spotted animals were given as a starting point the conclusion would be inevitable, that spotting should be considered dominant. Yet it is one and the same spotting in both cases. It is certain that "self" and "blaze" are alternative conditions, but it is equally certain that they differ from each other rather as two degrees of a single process, one greater, the other less, than as the presence and absence of one or more unit characters.

HAGEDOORN'S WORK

Hagedoorn's work shows the danger of the modern tendency to produce factors upon the slightest provocation. While adding, in experimental work, only a single litter of young bearing on the problem, he gives a symbol for a factor for dominant spotting in mice, and further considers it as due to a factor similar to that producing the dominant "English" spotting of rabbits. He refers to Morgan's work with black-eyed white and self mice as being a study of this dominant factor in mice. Morgan himself suggests that if black-eyed white mice represent the extremes of the spotted series the appearance of spotted animals in crosses with selfs is due to a *strengthening* of the spotting factor or to a *change* in dominance. This is far different from supposing the addition of an entirely new inhibiting factor comparable to the English pattern in rabbits. Cuénot with mice and Castle (1905) with guinea-pigs have shown that black-eyed whites *are* the extreme of the recessive spotted series and it is almost certain that Morgan's explanation of the results, as due to *a change in dominance,* is the correct one. It is, of course, obvious that the presence and absence hypothesis fails to explain any change of dominance of a single character.

To treat "dominant" spotting in mice as due to the presence of a definite unit-character is exceeding present experimental facts, while to consider it similar in nature to the "English" spotting of rabbits is still less justified.

One other point in Hagedoorn's work is of such a nature as to require further experimentation before it can be accepted.

This is the case (on page 126) of "mutual repulsion between two factors." In this case, Hagedoorn mated together agouti animals heterozygous in factor A (for color production) and in factor G (for the agouti pattern).

Such animals would ordinarily form gametes *AG, Ag, aG* and *ag* in equal numbers. These by independent recombination would form

$$\left.\begin{array}{l}1\ AAGG\\2\ AaGG\\2\ AAGg\\4\ AaGg\end{array}\right\}\text{9 agouti,}$$

$$\left.\begin{array}{l}1\ AAgg\\2\ Aagg\end{array}\right\}\text{3 black,}$$

$$\left.\begin{array}{l}1\ aaGG\\2\ aaGg\\1\ aagg\end{array}\right\}\text{4 albino.}$$

But Hagedoorn gives figures which show that the proportion which he obtains is nearer 2 agouti; 1 black and 1 albino. This he supposes to be due to the fact that *A* and *G* can never go into the same gamete.

Now let us see what happens if this is the case. The original heterozygotes will form only two kinds of gametes instead of four, these will be *aG* and *Ag*. Now in the recombination of these gametes the following result will be obtained.

$$\begin{array}{l}1\ aG\ aG = 1\text{ albino,}\\2\ aG\ Ag = 2\text{ agouti,}\\1\ Ag\ Ag = 1\text{ black.}\end{array}$$

So far, so good, but the trouble comes in testing the albinos. Here I may quote from Hagedoorn, p. 126:

> . . . thirteen of these albinos have been tested by mating with black. Without exception they have given black or equal numbers of black and albino young. . . . *But never has one of those albinos produced a single agouti young in a mating with black. Counting together the colored young of such families I get 89 black young.*[1]

This result is indeed remarkable, *for on Hagedoorn's own hypothesis* the albinos should have produced in such matings *nothing but agouti young,* ‘‘since they are all, by his hypothesis, homozygous for the agouti factor. The evidence is incontestable; *no repulsion of A and G can have occurred.* Has there been any coupling of these two factors? If such was the case only gametes *AG* and *ag* would have been formed and this would have given only *agoutis and albinos* in a 3:1 ratio, while Hagedoorn reports "73 agouti, *37 blacks*[1] and 32 albinos."

The case then is nothing so simple as "repulsion" or "coupling," it includes *failure to segregate and complete disappearance of a dominant Mendelian factor; G the factor for agouti.*

Since numerous investigators of color inheritance in mice have never found the agouti factor anything but a normal Mendelizing factor epistatic to black, and since Hagedoorn himself seems to have become mixed in his interpretation, it seems that the case proves or shows little until a satisfactory answer can be found to the question of what has become of the agouti factor.

Conclusions

The facts above given lead to the following conclusions:

1. The so-called dominant type of spotting in mice does not differ from "self" color by the presence of a unit character which "self" lacks. The presence and absence hypothesis fails to account for the shifting dominance seen in spotting in mice.
2. It is misleading to describe, under the same symbol, the so-called "dominant" spotting of mice and the English spotting in rabbits.
3. It seems probable that differences in "dominance" of spotting in mice are due to modifying supplementary factors and such spotting might be termed "unsuppressed" and "suppressed" spotting rather than "dominant" and "recessive" in the Mendelian sense.
4. Hagedoorn's hypothesis of repulsion between the color factor, *A*, and the agouti factor, *G*, is incorrect.

November 19, 1913.

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[1] Italics mine.